PATENT
Attorney Docket No. 67461-5041-US06 (Formerly 67229-13)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of DAHIYAT, *et al.* Serial No. 10/665,307 Filed: September 18, 2003 For: *Protein Design Automation for Protein Libraries*	Group No. 1631 Confirmation No. 6927 Examiner: DeJong, Eric S.

RESPONSE TO OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This paper is being submitted in response to the Office Action mailed September 22, 2006. This response is timely filed on or before February 22, 2006, with a petition for a two month extension of time. Although the Applicants do not believe any additional fees are required, the Commissioner is authorized to charge any additional fees, including extension fees or other relief, which may be required, or credit any overpayment to Deposit Account No. 50-0310 (Our order no. 67461-5041-US06).

Amendments to the Claims are reflected in the listing of claims, which begins on page 2.

Remarks begin on page 6.

Amendments to the Claims

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A method for generating a secondary library of protein sequences of a target protein comprising:

a) inputting the coordinates of said target protein into a computer;

b) utilizing said coordinates and a forcefield calculation to generate a primary library of primary protein sequences comprising a plurality of primary variant amino acid residues at primary variant positions;

c) generating a probability distribution of amino acid residues in a plurality of variant positions from said force field calculation; ~~and~~

d) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences; wherein at least one of said secondary protein sequences is different from said primary protein sequences; and

e) synthesizing a plurality of said secondary protein sequences.

2. (Currently Amended) A method ~~according to claim 1 wherein said combining comprises~~ for generating a secondary library of protein sequences of a target protein comprising:

a) inputting the coordinates of said target protein into a computer;

b) utilizing said coordinates and a forcefield calculation to generate a primary library of primary protein sequences comprising a plurality of primary variant amino acid residues at primary variant positions;

c) generating a probability distribution of amino acid residues in a plurality of variant positions from said force field calculation;

[a] d) generating a set of oligonucleotide probes each encoding at least one of said primary variant amino acid residues;

[b] e) using said probes in a polymerase chain reaction (PCR) to generate a plurality of oligonucleotide sequences, each encoding a plurality of said secondary variant protein sequences, wherein at least one of said secondary variant protein sequences is different from said primary protein sequences; and,

[c] f) producing said secondary variant protein sequences in host cells transformed with said oligonucleotide sequences.

3. (Previously Presented) A method according to claim 2 wherein said PCR is multiple PCR and wherein said probes are pooled.

4. (Previously Presented) A method according to claim 3 wherein said probes are added in equimolar amounts.

5. (Previously Presented) A method according to claim 3 wherein said probes are combined in amounts that correspond to the probability of said variant amino acid residues in said probability distribution table.

6. (Cancelled)

7. (Previously Presented) A method according to claim 1 wherein said target protein is an enzyme.

8. (Previously Presented) A method according to claim 1 wherein said target protein is a therapeutic protein.

9. (Previously Presented) A method according to claim 1 wherein the coordinates of a region surrounding a binding site to a receptor is input into a computer.

10. (Previously Presented) A method according to claim 1 wherein said primary variant positions comprise a region surrounding a binding site.

11. (Previously Presented) A method according to claim 8 wherein said primary variant positions comprise a region surrounding a binding site to a receptor.

12. (Previously Presented) A method according to claim 7 wherein said primary variant positions comprise a region surrounding the active site of said enzyme.

13. (Previously Presented) A method according to claim 7 wherein said primary variant positions comprise a region surrounding the catalytic residues of said enzyme.

14. (Currently Amended) A method for generating a secondary library of protein sequences of a target protein comprising:

(A) generating a primary library comprising:

(i) inputting the coordinates of a target protein with variable residue positions;

(ii) establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue position comprises at least two different amino acid side chains; and

(iii) analyzing the interaction of each of said amino acids with plurality of said amino acids at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences;

(B) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences; ~~and~~

(C) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants; and

(D) synthesizing a plurality of said secondary protein sequences;

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

15. (Currently Amended) A method for generating a secondary library of protein sequences of a target protein comprising:

(A) generating a primary library comprising:

(i) inputting the coordinates of a target protein with variable residue positions;

(ii) establishing a group of potential rotamers for each of said variable residue positions,

wherein the group of potential rotamers for at least one of said variable residue position has a rotamer selected from each of at least two different amino acid side chains; and

(iii) analyzing the interaction of each of said rotamers with plurality of said rotamers at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences;

(B) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences; ~~and~~

(C) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants; and,

(D) synthesizing a plurality of said secondary protein sequences.

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

16. (Previously Presented) A method according to claim 14, wherein said force field calculation is Self-Consistent Mean Field (SCMF).

17. (Currently Amended) A method for generating a secondary library of protein variants of a target protein comprising:

(A) generating a primary library comprising:

(i) inputting the coordinates of a target protein with variable residue positions;

(ii) establishing a group of potential rotamers for each of said variable residue positions, wherein the group of potential rotamers for at least one of said variable residue position has a rotamer selected from each of at least two different amino acid side chains; and

(iii) analyzing the interaction of each of said rotamers with plurality of said rotamers at a plurality of variable residue positions and all or part of the remainder of said protein to generate a primary library of primary sequences optimized for at least one scoring function;

(B) generating a probability distribution of amino acid residues from said primary library in a plurality of variant positions from said primary sequences; ~~and~~

(C) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences comprising secondary variants; wherein at least one of said secondary variants is different from said primary variants;and,

(D) synthesizing a plurality of said secondary protein sequences.

wherein at least one of said analyzing, generating or combining steps comprises using a force field calculation.

18. (Previously Presented) A method according to claim 17, wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

19. (Previously Presented) A method according to claim 14, 15, or 17, wherein said analyzing step utilizes a force field calculation.

20. (Previously Presented) A method according to claim 14, 15, or 17, wherein said generating step (B) utilizes a force field calculation.

21. (Previously Presented) A method according to claim 14, 15, or 17, wherein said combining step utilizes a force field calculation.

22. (Currently Amended) A method for generating a secondary library of protein sequences of a target protein comprising:

a) inputting the coordinates of said target protein into a computer;

b) specifying a list of at least two primary variant positions;

c) utilizing said coordinates and a forcefield calculation to generate a primary library comprising a plurality of primary variant amino acid residues at said primary variant positions;

d) generating a probability distribution of amino acid residues in a plurality of variant positions from a force field calculation; ~~and~~

e) combining a plurality of said amino acid residues from said probability distribution to generate a secondary library of secondary sequences; wherein at least one of said secondary protein sequences is different from said primary protein sequences; and,

f) synthesizing a plurality of said secondary protein sequences.

23. (Previously Presented) A method according to claim 22 wherein said primary library is generated using a monte carlo search.

24. (Previously Presented) A method according to claim 22 wherein said primary library is generated using a genetic algorithm.

25. (Previously Presented) A method according to claim 22 wherein said probability distribution table is derived from frequencies of occurrence in a primary variant library.

26. (Previously Presented) A method according to claim 1 wherein combining said plurality of said amino acid residues from said probability distribution comprises a calculation in said computer.

REMARKS

Claims 1, 2, 14, 15, 17 and 22 have been amended Claims 1-5 and 7-26 are pending. Inventorship is not changed by these amendments.

Response to Objection of claims 2-5

Claims 2 is objected to as expanding the scope of independent claim 1. While applicants respectfully disagree, in an effort to further prosecution, claim 2 has been rewritten in independent form as suggested by the Examiner.

Response to Rejection under 35 USC § 101

Claims 1 and 7-26 are rejected under 35 USC § 101 as not producing a tangible result. Without admitting the propriety of the rejection, and in the interests of furthering the prosecution, independent claims 1, 14, 15, 17 and 22 have been amended to include a physical transformation, as suggested by the Examiner. Specifically, these independent claims now require synthesizing a plurality of secondary protein sequences. Applicants note that claim 2 also requires a physical transformation. Specifically, claim 2 requires producing secondary variant protein sequences in host cells transformed with oligonucleotide sequences.

The Applicants submit that in light of the above amendments and response, the claims are now in condition for allowance and an early notification of such is respectfully solicited. The Examiner is invited to contact the undersigned at (415) 442-1000 if any issues may be resolved in that manner.

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. 1.6(a)(4)
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Dated: February 22, 2007
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MORGAN, LEWIS & BOCKIUS LLP

Dated: 2/22/07

/ Robin Silva /
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